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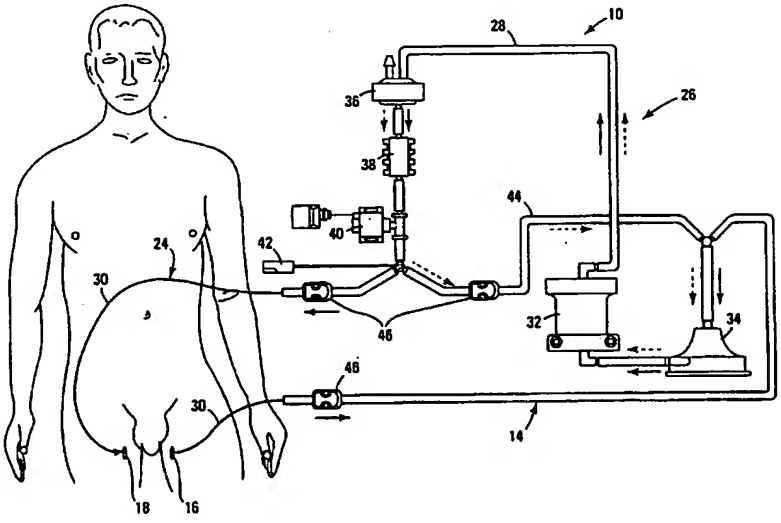
(54) Title: TREATMENT OF HIV USING HYPERTHERMIA



(57) Abstract: The invention provides a method for treating a patient infected with human immunodeficiency virus (HIV) comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time, wherein the core temperature is raised to a temperature range and a duration sufficient to: (1) eliminate or reduce viable HIV to an extent such that a culture of HIV from the patient is negative around three months after the core temperature of the patient has been raised and returned to normal at least one time and (2) result in an increase in the CD8 % around one month after the core temperature of the patient has been raised and returned to normal at least one time.

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duration sufficient to: (1) eliminate or reduce viable HIV to an extent such that a culture of HIV from the patient is negative around three months after the core temperature of the patient has been raised and returned to normal at least one time and (2) result in an increase in the CD8% around one month after the core temperature of the patient has been raised and returned to normal at least one time.

The invention also provides a method for auto-inoculating a patient infected with human immunodeficiency virus (HIV) comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time. The core temperature is raised to a temperature range and a duration sufficient to: (1) eliminate or reduce viable HIV to an extent such that a culture of HIV from the patient is negative around three months after the core temperature of the patient has been raised and returned to normal at least one time and (2) result in an increase in the CD8% around one month after the core temperature of the patient has been raised and returned to normal at least one time, and the patient has a measurable viral load of HIV around three months after the core temperature of the patient has been raised and returned to normal at least one time.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a simplified perspective view of an apparatus used to practice the invention.

FIG. 2 is a mechanical diagram showing cannulation sites on a human adult.

FIG. 3 is a simplified diagram of the system illustrated in FIG. 2.

FIG. 4 is a cross-section of a temperature sensor.

FIG. 5 is a cross-section of a temperature catheter having a temperature sensor positioned at the urinary sphincter muscle with the aid of an inflatable cuff that engages the bladder wall.

FIG. 6 is a cross-section of temperature catheter having two temperature sensors, one of which is positioned at the urinary sphincter muscle with the aid of an inflatable cuff that engages the bladder wall and the second of which is positioned in the urine pool.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a method for treating a patient infected with human immunodeficiency virus (HIV) comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time. The core temperature is raised to a temperature range, a duration, and a number of times sufficient to: (1) eliminate or reduce viable HIV to an extent such that a culture of HIV from the patient is negative around three months after the core temperature of the patient has been raised and returned to normal at least one time and (2) result in an increase in the CD8% around one month after the core temperature of the patient has been raised and returned to normal at least one time. "Treating" in this application means raising the core temperature to a temperature range, a duration, and a number to times sufficient to: (1) eliminate or reduce viable HIV to an extent such that a culture of HIV from the patient is negative around three months after the core temperature of the patient has been raised and returned to normal at least one time and (2) result in an increase in the CD8% around one month after the core temperature of the patient has been raised and returned to normal at least one time.

"Returning the core temperature of the patient to normal" includes allowing the patient to cool through ambient heat loss and actively cooling the patient. In the examples described below, the patient is cooled by ambient heat loss and active cooling to a temperature of 39°C. The patient is released from the hospital and the patient's temperature gradually returns to normal (37°C) over a period of a few days. In one embodiment, the core temperature of the patient is raised and returned to normal one time. In another embodiment, the core temperature of the patient is raised and returned to normal two or more times. In one embodiment, the core temperature is raised by circulating the patient's blood from the patient, through an extracorporeal blood flow circuit, and back to the patient, wherein the blood returned to the patient has been heated within the blood flow circuit to an elevated temperature range. The patient's blood can be circulated from the patient through a blood vessel and returned to the patient through a blood vessel. In one embodiment, the patient's blood is circulated from the patient through a vein and returned to the patient through a vein. In another embodiment, the patient's blood is circulated from the patient through an artery and returned to the patient through a vein. In another embodiment, the core temperature is raised by inserting a heating element into the patient and the heating element heats the patient's blood. The heating element can be inserted into a blood vessel of the patient.

The heating element can be inserted into a central vessel, i.e., aorta or vena cava, where it can heat the blood passing by and eventually heating the blood to such a degree that the net temperature gain exceeds the losses due to the normal (physiologic) cooling mechanisms. Over time the body temperature can be raised to a predetermined point and maintained for a predetermined time. The heating element can be housed within a sheath or catheter at one or multiple positions along its length. The sheath or catheter can contain wires, conduits, fiberoptic, or other materials to supply power to the heating element. External to the body there could be a plug to connect the sheath or catheter to the control system. The sheath or catheter can be treated to give it antithrombogenic properties. This treatment can be chemical or a high energy corona or plasma discharge in the presence of a monomeric gas. The method of insertion can be through a cut-down or percutaneously (Seldinger Technique).

The heating element's method of heating can be by an electrical heating, radiofrequency, or laser. The heating element should not exceed 50°C at the surface that contacts blood.

Such a heating element can be used for core heating and can also be used for local or regional heating. For example, a percutaneous insertion into an artery with a hollow sheath or catheter can be made to accommodate a steering guidewire so the device can be placed into the hepatic artery. A second hollow catheter with a thermistor tip can be placed, via a venous percutaneous stick, into the hepatic vein for liver temperature.

Methods which heat the blood to raise the core temperature, such as extracorporeal whole body hyperthermia, are preferred. However, methods in which the core temperature is raised by other methods such as by infrared radiation, convection, or surface contact such as a heating blanket can also be used in the method of the invention.

The core temperature can be raised to a temperature range of from 38 to 48°C , more preferably 38 to 44°C, more preferably 41.8 to 42.2°C. The core temperature can be raised for a period of from 2 minutes to sixteen hours, a period of from one-half to three hours, a period of from one to two hours, a period of from 80 to 100 minutes, or for 90 minutes. The core temperature can be taken rectally. For purposes of this application, the "core temperature" means rectal temperature. Temperatures other than the rectal temperature can be taken in the practice of the invention, e.g., esphogeal, bladder, tympanic, or cardiac line temperatures. The relationship between such other temperatures and the rectal temperature is well known in the art and such measurement by other methods will allow determination of the core temperature as defined herein.

Recommended exposure times during extracorporeal whole body hyperthermia are given in Table 1 below.

TABLE 1

Core Temperature (°C)	Exposure (minutes)
39	960
40	480
41	240
42	120
43	60
44	30
45	15
46	8
47	4
48	2

The patient's viral load of HIV can be determined at least once before the core temperature has been raised at least one time; at least once after the core temperature has been raised and returned to normal at least one time; at least two different times after the core temperature has been raised and returned to normal at least one time, or combinations thereof.

In embodiments of the invention, the patient is failing multi-pharmaceutical treatment for HIV; in other embodiments, the patient is not failing multi-pharmaceutical treatment for HIV. If the patient is not failing multi-pharmaceutical treatments, the patient can still benefit from the hyperthermia treatment because the patient can go on a "drug holiday" (strategic treatment interruptions) to give the patient time to recover from the side effects (such as mitochondrial damage) of the multi-pharmaceutical treatment for HIV.

In one embodiment of the invention, the CD8% has increased 5 percent or more one month after the core temperature of the patient has been raised and returned to normal said at least one time; in other embodiments, the CD8% has increased 10 percent or more or 20 percent or more one month after the core temperature of the patient has been raised and returned to normal said at least one time. For instance, by the phrase "the CD8% has increased 5 percent" is meant that the relative CD8% has increased 5 percent—not that the absolute CD8% has increased 5 percent. In embodiments of the invention, CD8% is measured before raising the core temperature of the patient and after the core temperature of the patient has been raised and returned to normal said at least

one time. In other embodiments, the CD8% is measured around one day or around one month after the core temperature of the patient has been raised and returned to normal said at least one time.

In embodiments of the invention, the ability to culture HIV from the patient is assessed from around three months to around six months after the core temperature has been raised and returned to normal said at least one time.

In embodiments of the invention, a culture of HIV from the patient is negative around six months after the core temperature has been raised and returned to normal said at least one time; in other embodiments, a culture of HIV from the patient is negative around one year or around two years after the core temperature has been raised and returned to normal said at least one time.

The invention provides a method for auto-inoculating a patient infected with human immunodeficiency virus (HIV) comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time. The core temperature is raised to a temperature range and a duration sufficient to: (1) eliminate or reduce viable HIV to an extent such that a culture of HIV from the patient is negative around three months after the core temperature of the patient has been raised and returned to normal at least one time and (2) result in an increase in the CD8% around one month after the core temperature of the patient has been raised and returned to normal at least one time, and the patient has a measurable viral load of HIV around three months after the core temperature of the patient has been raised and returned to normal at least one time.

While not wishing to be bound by theory, the inventors think it likely that the hyperthermia upregulates HIV from reservoirs within the body and results in the HIV being put into the blood. This circulating HIV causes a reaction in the cell mediated immunity arm and can cause activation of CD4 and CD8 cells specific against the circulating virus. Heat damaged/nonviable HIV may also act as a vaccine, stimulating B-cells to form antibodies and the cell mediated arm may cause T-cell responses to the specific HIV fragments or nonviable virus, further enhancing immunity. Traditional vaccines do not appear to be very effective due to HIV's tendency to mutate rapidly. In addition, the hyperthermia treatment appears to stimulate CD8 suppressor cells that may assist in providing virological control, especially CD8 cells specific for HIV.

In embodiments of the invention, a culture of HIV from the patient is negative and the patient has a measurable viral load of HIV around six months after the core temperature has been raised and returned to normal said at least one time; in other embodiments, a culture of HIV from the patient is negative

and the patient has a measurable viral load of HIV around one year or around two years after the core temperature has been raised and returned to normal said at least one time. In embodiments of the invention, the viral load of HIV is measured using a reverse transcriptase-polymerase chain reaction test at these times or other times.

In embodiments of the invention, the patient's viral load of HIV is determined at least once before the core temperature has been raised said at least one time. In embodiments of the invention, the patient's viral load of HIV is determined at least once after the core temperature has been raised and returned to normal said at least one time.

The method of the invention can further comprise treating the patient with a pharmaceutical indicated for HIV.

The pharmaceutical can be administered more than three months after the core temperature of the patient has been raised and returned to normal at least one time. In embodiments of the invention, the raising the core temperature of the patient and then returning the core temperature of the patient to normal is alternated with treating the patient with the pharmaceutical. In embodiments of the invention, at some time subsequent to three months after the core temperature of the patient has been raised and returned to normal at least one time, a culture of HIV from the patient is positive and the patient is then treated with a pharmaceutical indicated for HIV. Preferably, the patient is not treated with any pharmaceuticals indicated for HIV for at least one month after the core temperature of the patient has been raised and returned to normal—this allows the patient to go on a drug holiday and recover from the side effects of the pharmaceuticals indicated for HIV.

In other embodiments of the invention, at some time subsequent to three months after the core temperature of the patient has been raised and returned to normal at least one time, a culture of HIV from the patient is positive and the patient is then re-treated with the method for treating a patient infected with HIV.

The efficacy of a pharmaceutical effective for treatment of HIV in some patients can be increased when combined with hyperthermia. The method of the invention can also comprise treating the patient with a pharmaceutical indicated for HIV where such pharmaceutical was not efficacious for stand alone treatment for HIV and when combined with hyperthermic treatment results in the pharmaceutical being efficacious in some patients. The patient can be treated with a single pharmaceutical effective against HIV or with two or more pharmaceuticals effective against HIV. The drug can be administered to the

same patient at several points: before raising the core temperature of the patient at least one time, while the core temperature of the patient is raised, and after the core temperature of the patient has been raised and returned to normal at least one time, or combinations thereof.

The pharmaceutical can be selected from interferons, protease inhibitors, cytokines, nucleoside analog reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, or any combination of antiviral drugs. The pharmaceutical can be selected from ribavirin, lamivudine, interferon alfacon-1, interferon alfa-2a, interferon alfa-2b, interferon-alfa-nl, thymosin alpha-1, interleukin-2, interferon alpha-n3, ketoprofen, interferon beta-la, interferon gamma-1b, interleukin-12, histamine dihydrochloride, thymalfasin, zidovudine, didanosine, zalcitabine, stavudine, abacavar, nevirapine, delaviridine, efavirenz, ritonavir, indinavir, nelfinavir, saquinavir, amprenavir, or combinations thereof. In a preferred embodiment, the pharmaceutical can be selected from an interferon, ribavirin, or lamivudine. In another preferred embodiment, the pharmaceutical is an alpha interferon. The pharmaceutical can also include antioxidants, non-steroidal anti-inflammatory drugs, and/or reactive oxygen free radical scavengers. Several pharmaceuticals are being studied and some are available for treatment of HIV. Cytokine addition can be used either to prepare the immune system prior to hyperthermia or after treatment to supplement the effects of the hyperthermia.

The patient infected with HIV might have an acute HIV infection or a latent HIV infection. The patient might be co-infected with a pathogen. The pathogen might be a virus, a spirochete, or a bacterium. The virus might be a heat labile virus. The heat labile virus might be selected from herpesviruses, hepadnaviruses, togaviruses, flaviviruses, coronaviruses, rhabdoviruses, filoviruses, paramyxoviruses, othomyxoviruses, bunyaviruses, arenaviruses, or retroviruses. The heat labile virus might be hepatitis B virus, hepatitis C virus, Epstein-Barr virus, cytomegalovirus, or varicella-zoster virus. In a preferred embodiment, the heat labile virus is HIV. The spirochete might be from the genus treponema, borrelia, or leptospira. The spirochete might be *Treponema pallidum, Treponema pertenue, Treponema carateum, Treponema pallidum endemicum, Borrelia burgdorferi, Borrelia hermsii,* or *Leptospira interrogans*. The bacterium might be an aerobic or anaerobic bacterium.

The invention also provides a method for treating a patient infected with HIV comprising raising the temperature of the patient's liver and then returning the temperature of the patient's liver to normal at least one time. The temperature of the patient's liver is raised to a temperature range, a duration, and

a number of times sufficient to: (1) eliminate or reduce viable HIV to an extent such that a culture of HIV from the patient is negative around three months after the core temperature of the patient has been raised and returned to normal at least one time and (2) result in an increase in the CD8% around one month after the core temperature of the patient has been raised and returned to normal at least one time. In embodiments of the invention, the temperature of the liver is raised by local, regional, or intraperitoneal hyperthermia. In addition, the liver can be heated by the methods for raising the core temperature that are described herein.

Conventional hyperthermia equipment can be used in the methods of the invention.

A number of different tests are used to determine if a person has been infected with HIV. Clinicians will test specifically for HIV. One set of tests looks for the presence of antibodies to HIV. If the antibodies (also referred to as anti-HIV) are present in a person's blood, it usually means that the person has been infected with HIV.

Other tests that are frequently performed detect the presence of HIV RNA. The two tests that are used to measure HIV RNA are called the reverse transcriptase-polymerase chain reaction (RT-PCR) test and the branched chain DNA (bDNA) test. RT-PCR is a more sensitive test and can detect much lower amounts of the virus than the bDNA test. The bDNA test can detect large numbers of the virus in the blood, but cannot detect the virus if only a low amount of the virus is present.

EXAMPLES

Several HIV/AIDS patients who were failing or had failed HIV pharmaceutical therapies were treated. The patients received a session of Extracorporeal Whole Body Hyperthermia (EWBH). The patients continued their HIV drug regimens until the hyperthermia treatment and discontinued their drug regimens for the treatment and follow-up period.

The patients were failing pharmaceutical therapy, as defined by (A) an HIV PCR viral load $\geq$ 10,000 on a stable antiviral regimen, and (B) the failure of two or more combination antiviral regimens composed of all three of the following categories: two nucleoside analogues, one non-nucleoside reverse transcriptase inhibitor and one protease inhibitor. The patients underwent a single hyperthermic treatment in which their core body temperature was raised to a maximum of 41.8 $\pm$ 0.2°C for 90 minutes.

Table 2 below presents the results of the EWBH treatments of seven patients. Table 3 below presents the results for nine control patients, and Table 4

presents the results for two control patients that were subsequently treated with EWBH and one patient who was re-treated with EWBH.

TABLE 2
TREATED PATIENT DATA

Patient	Interval Date	HIV Viral Load	CD4	CD4%	CD8	CD8%	Bilirubin	Platelets	ALT	AST	HCV Viral Load	Re-Test
Patient 1												
Baseline	0	237,112	38	4	733	78	0.9	135,000	127	148		
Day 1	1	Inhibitory	11	6	130	72	1.9	Inhibitory	1,995	2,529		
Day 3-7	5	659,208	33	4	549	67	2.8	66,000	1,565	891		
Month 1	27	215,221	25	3	647	78	0.6	138,000	58	75		
Month 2	59	293,659	24	2	854	70	0.8	Inhibitory	85	104		
Unsch	90	305,447	23	4	708	73	5.9	147,000	59	67		
Month 4	123	215,761	23	1	1005	62	0.7	272,000	84	95		
Unsch	154	216,279	cancelled lipemic				1.0	195,000	100	91		
Month 6	181	440,954	11	1	464	51	0.6	126,000	85	98		
Patient 2	Re-treat; Genotype 1b											
Baseline	0	60,981	108	20	335	62	1.0	94,000	95	73	14.3	
Day 1	1	249,289	100	25	164	41	1.4	21,000	325	421	ND	
Day 3-7	3	100,641	72	30	122	51	1.1	43,000	531	186	38.3	
Unsch	24	69,021	102	12	689	81	ND	80,000	100	64	8.38	
Month 1	33	37,813	112	13	611	71	0.9	147,000	97	65	5.26	
Unsch	45	70,632	133	14	665	70	0.9	109,000	97	74	7.32	
Month 2	59	62,044	111	14	498	63	0.7	108,000	88	75	1.36	
Unsch	73	150,142	123	15	501	60	1.2	76,000	78	57	0.65	
Unsch	88	196,237	101	11	559	62	1.4	87,000	69	59	<0.20	178,000 copies/ml
Unsch	102	134,415	ND	ND	ND	ND	ND	ND	ND	ND	<0.20	
Month 4	116	206,852	115	10	775	66	1.1	98,000	61	57	0.32	159,000 copies/ml

TABLE 2
TREATED PATIENT DATA

Patient	Interval Date	HIV Viral Load	CD4	CD4%	CD8	CD8%	Bilirubin	Platelets	ALT	AST	HCV Viral Load	Re-Test
Patient 3												
Baseline	0	104,922	22	5	290	66	0.4	124,000	31	24		
Day 1	1	745,156	12	12	41	41	1.0	39,000	139	241		
Day 3-7	10	86,309	22	3	533	73	0.9	253,000	79	34		
Month 1	27	116,023	14	6	146	61	1.2	108,000	45	34		
Month 2	60	235,837	13	8	112	64	2.9	191,000	55	48		
Unsch	95	322,916	11	4	114	45	0.6	152,000	122	90		
Patient 4												
Baseline	0	24,619	202	11	1251	68	0.7	206,000	16	27		
Day 1	1	71,327	86	10	747	47	0.5	107,000	84	98		
Day 3-7	3	57,262	143	9	447	52	0.5	165,000	73	64		
Month 1	32	20,751	149	10	931	62	0.6	197,000	18	23		
Month 2	64	66,230	205	11	1151	60	0.5	219,000	22	31		
Unsch	92	46,974	189	10	1166	63	0.8	244,000	23	26		
Month 4	122	45,012	128	8	1040	63	0.6	212,000	20	25		
Unsch	156	138,248	91	9	636	63	0.7	225,000	22	29		
Month 6	184	98,830	75	7	691	63	0.7	232,000	27	27		
Patient 5												
Baseline	0	74,902	121	7	1465	80	0.4	55,000	21	28		
Day 1	1	750,000	inhibitory	inhibitory	inhibitory	inhibitory	3.6	inhibitory	610	959		
Day 3-7	3	618,067	35	13	151	56	4.8	32,000	814	978		
Month 1	36	21,098	79	6	1108	80	0.6	cancelled hemolzed	46	32		
Month 2	71	157,621	62	5	1081	83	0.8	123,000	23	27		
Unsch	99	121,561	52	6	612	75	0.6	135,000	27	24		
Month 4	127	510,677	46	5	692	75	0.9	62,000	30	28		
Unsch	155	737,657	19	3	509	80	1.0	low	18	27		
Month 6	183	641,739	15	3	412	79	1.0	44,000	28	38		

TABLE 2
TREATED PATIENT DATA

Patient	Interval Date	HIV Viral Load	CD4	CD4%	CD8	CD8%	Bilirubin	Platelets	ALT	AST	HCV Viral Load	Re-Test
Patient 6	Genotype 1a											
Baseline	0	157,599	7	2	189	51	0.4	hemolzed	60	82	1.1	
Day 1	1	410,332	4	3	96	63	0.7	hemolzed	214	439	11.7	
Day 3-7	3	619,376	9	6	79	53	1.4	34,000	125	199	14.0	
Month 1	32	472,724	10	2	348	58	0.5	62,000	42	64	2.17	
Unsch	51	ND	ND	ND	ND	ND	ND	ND	ND	ND	13.5	
Month 2	60	400,902	7	1	296	58	0.5	86,000	38	52	5.24	
Unsch	87	405,932	6	2	178	54	0.6	low	74	85	5.5	
Month 4	115	580,494	4	2	132	60	0.9	50,000	77	80	8.3	
Unsch	150	>750,000	4	1	149	52	1.5	75,000	58	72	5.51	
Month 6	178	>750,000	4	2	141	61	0.6	84,000	53	64	9.17	
Patient 7												
Baseline	0	NA	345	11	2081	67	0.3	105,000	116	67		
Day 1	0	24,116	73	15	132	28	2.1	11,000	542	545		

TABLE 2
TREATED PATIENT DATA

MEAN	HIV Viral Load	CD4	CD4%	CD8	CD8%	Bilirubin	Platelets	ALT	AST	# patients at time interval	HCV Viral Load	# patients at time interval	
Baseline										8	7.70	2	
Day 1	375,037	48	12	218	49	1.60	44,500	558	747	7	11.70	1	
Days 3-7	356,811	52	11	314	59	1.92	98,833	531	392	6	26.15	2	
Unsch	69,021	102	12	689	81	0.00	80,000	100	64	1	8.38	1	
Month 1	147,272	65	7	632	67	0.73	130,400	51	49	6	3.72	2	
Unsch	70,632	133	14	665	70					2	7.32	1	
Month 2	206,571	70	7	665	66	1.03	145,400	52	56	6	3.43	2	
Unsch	225,495	67	7	547	62	1.62	150,800	64	58	6	3.08	2	
Unsch	196,237	101	11	559	62	1.20	87,000	69	59	1	0.00	1	
Month 4	311,759	63	5	729	65	0.84	138,800	54	57	5	1.09	2	
Unsch	364,061	38	4	431	65	0.68	165,000	35	40	3	0.65	1	
Month 6	393,841	26	3	427	64	0.73	121,500	48	56	4	9.17	1	

TABLE 3
CONTROL PATIENT DATA

Patient ID	Interval Date	HIV Viral Load	CD4	CD4%	CD8	CD8%	Bilirubin	Platelets	ALT	AST	HCV Viral Load	Re-Test
Patient 8	Crossover-1st treat											
Baseline	0	36,603	169	14	668	55	1.7	188,000	19	38		
Day 3-7	6	47,443	207	14	799	59	0.4	166,000	14	23		
Month 1	33	28,721	194	13	798	58	1.0	168,000	14	19		
Month 2	70	71,546	154	8	818	32	0.5	161,000	14	21		
Unsch	96	139,826	159	12	698	53	0.6	155,000	13	23		
Unsch	103	177,896	NA	NA	NA	NA	NA	NA	NA	NA		
Patient 9												
Baseline	0	125,985	7	1	354	52	0.3	125,000	31	22		
Day 3-7	21	75,782	9	1	381	41	0.5	124,000	22	21		
Patient 10	Eligible for re-treatment											
Baseline	0	167,782	0	0	65	21	1.4	179,000	65	44		
Day 3-7	7	11,896	3	1	77	24	0.6	190,000	55	38		
Month 1	42	245,123	3	1	52	20	0.4	180,000	81	40		
Month 2	68	357,122	2	1	49	21	0.4	174,000	55	39		
Unsch	98	286,966	2	1	71	22	0.4	243,000	45	38		
Month 4	190	13,256	3	1	81	21	0.4	354,000	96	70		

TABLE 3
CONTROL PATIENT DATA

Patient	Interval Date	HIV Viral Load	CD4	CD4%	CD8	CD8%	Bilirubin	Platelets	ALT	AST	HCV Viral Load	Re-Test
Patient 11	Crossover 1st treat											
Baseline	0	29,914	279	15	1190	64	0.7	207,000	38	36		
Days 3-7	0	34,827	304	17	1020	57	0.5	205,000	31	32		
Month 1	27	37,374	258	17	942	62	0.9	inhibitory	45	43		
Month 2	55	123,015	302	14	1234	57	0.6	214,000	40	28		
Unsch	61	134,815	NA	NA	NA	NA	NA	NA	NA	NA		
Patient 12												
Baseline	0	104,339	79	8	693	70	0.6	115,000	49	41		
Days 3-7	6	82,044	97	6	1143	71	0.7	inhibitory	51	43		
Month 1	29	157,814	98	5	992	48	0.5	146,000	66	38		
Month 2	64	163,333	76	4	863	46	0.6	173,000	73	52		
Unsch	103	130,469	76	5	690	48	0.6	160,000	64	53		
Month 4	127	130,117	73	5	797	51	2.3	129,000	89	59		
Unsch	155	156,468	61	4	740	44	0.6	214,000	64	52		
Month 6	200	110,063	68	4	776	46	1.4	188,000	60	43		
Patient 13												
Baseline	0	19,284	8	4	114	63	0.4	158,000	16	17		
Days 3-7	7	19,636	14	4	157	46	0.6	223,000	12	18		
Month 1	28	33,805	15	5	148	47	1.0	234,000	14	23		
Month 2	56	53,496	16	5	148	47	0.6	normal	15	22		
Unsch	84	56,729	8	5	83	55	0.4	164,000	23	23		
Month 4	112	54,438	6	4	115	78	0.6	200,000	13	21		
Unsch	140	8,215	4	5	72	85	1.9	105,000	135	99		
Unsch	154	14,337	8	3	177	62	2.0	190,000	89	150		

TABLE 3
CONTROL PATIENT DATA

Patient	Interval Date	HIV Viral Load	CD4	CD4%	CD8	CD8%	Bilirubin	Platelets	ALT	AST	HCV Viral Load	Re-Test
Patient 14	Genotype-1a											
Baseline	0	486,088	4	1	138	49	0.5	120,000	108	87	20.2	
Days 3-7	8	132,784	4	1	154	43	1.0	111,000	107	89	9.06	
Month 1	28	199,091	2	1	136	48	0.9	105,000	106	85	12.2	
Month 2	55	207,950	2	1	90	42	0.6	180,000	116	150	13.2	
Unsch	83	146,000	2	1	116	46	0.7	91,000	114	95	6.9	
Month 4	111	187,714	3	1	378	70	0.8	123,000	87	95	11.6	
Unsch	145	278,077	2	0	658	78	0.9	114,000	82	64	10.9	
Month 6												
Patient 15												
Baseline	0	17,901	106	16	319	48	0.3	191,000	22	28		
Days 3-7	7	28,107	161	18	464	53	0.4	205,000	19	30		
Month 1	28	34,919	122	15	410	52	0.6	185,000	33	32		
Month 2	56	18,914	175	17	616	59	1.1	238,000	37	37		
Unsch	84	42,803	143	15	616	64	0.4	169,000	31	33		
Month 4	112	47,873	138	14	595	61	0.4	200,000	26	27		
Month 6												
Patient 16	Genotype- 3a											
Baseline	0	192,874	42	9	232	50	1.0	162,000	66.0	50	12.4	
Days 3-7	7	211,115	31	5	244	43	1.3	161,000	86.0	53	9.67	
Month 1	33	131,425	31	8	181	45	0.9	116,000	59	45	8.87	
Month 2	63	46,613	31	6	223	44	0.7	Hemolyzed	72	46	10.2	
Unsch	97	97,418	40	5	433	49	0.7	131,000	60	47	3.3	
Month 4	130	158,395	24	6	160	39	0.7	103,000	49	39	<0.20	
Month 6												

TABLE 3
CONTROL PATIENT DATA

MEAN	HIV Viral Load	CD4	CD4%	CD8	CD8%	Bilirubin	Platelets	ALT	AST	# patients at time interval	HCV Viral Load	# patients at time interval	
Baseline	131,197	77	8	419	52	1	160,556	46	40	9	10.10	2	
Days 3-7	71,515	92	7	493	49	1	173,125	44	39	9	9.06	1	
Month 1	108,534	90	8	457	48	1	162,000	52	41	8	6.10	2	
Month 2	130,249	95	7	505	44	1	190,000	53	49	8	11.70	2	
Unsch	138,148	61	6	387	48	1	159,000	50	45	8	5.10	2	
Unsch	177,896	0	0	0	0	0	0	0	0	1		0	
Month 4	115,707	41	5	354	53	1	184,833	60	52	6	11.60	1	
Unsch	114,004	22	3	490	69	1	144,333	94	72	3	10.90	1	
Unsch	14,337	8	3	177	62	2	190,000	89	150	1			
Month 6	110,063	68	4	776	46	1	188,000	60	43	1			

TABLE 4
RE-TREATMENT PATIENT DATA

Patient ID	Interval Date	HIV Viral Load	CD4	CD4%	CD8	CD8%	Bilirubin	Platelets	ALT	AST	HCV Viral Load	Re-Test
Patient 8	Crossover-1st treat											
Baseline	0	83,712	102	11	426	11	0.3	125,000	11	27		
Day 1	1	Indeterminate		36	14	104	41	1.4	70,000	194	337	
Day 3-7	8	143,031	118	11	733	67	0.8	251,000	149.0	33		
Month 1	29	205,675	159	11	903	65	0.5	101,000	15	20		
Month 2	33	146,328	130	13	577	58	1.6	138,000	14	23		
Unsch	90	180,846	106	11	543	57	0.6	132,000	16	22		
Month 4	125	566,165	72	9	437	55	1.3	115,000	26.0	27		
Unsch	153	250,934	51	6	434	53	0.5	114,000	21.0	28		
Month 6												
Patient 11	Crossover-1st treat											
Baseline	0	274,094	140	10	574	43	0.4	263,000	35	35		
Day 1	1	713,979	95	23	155	37	0.5	26,000	528	585		
Day 3-7	9	207,783	138	13	620	60	0.6	329,000	281.0	47		
Month 1	27	497,812	133	14	596	61	0.7	174,000	70	45		
Month 2	58	475,606	164	11	920	60	1.2	339,000	56	48		
Unsch	86	508,903	159	9	1038	58	1.1	245,000	52	64		
Month 4	113	311,843	132	10	748	55	0.5	270,000	74.0	56		
Unsch	141	389,609	117	8	944	65	0.4	241,000	59.0	63		
Month 6												
Patient 2	Re-Treat-Genotype 1b											
Baseline	0	313,056	50	6	496	59	0.7	71,000	98	61	2.5	
Day 1	1	750,000	33	13	113	46	2.2	15,000	986	1,567	0.9	

TABLE 4
RE-TREATMENT PATIENT DATA

MEAN	HIV Viral Load	CD4	CD4%	CD8	CD8%	Bilirubin	Platelets	ALT	AST	# patients at time interval	HCV Viral Load	# patients at time interval	
Baseline	223,621	92	9	371	38	0.47	153,000	48	41	3	2.50	1	
Day 1	731,990	55	17	124	41	1.37	37,000	569	830	3	0.90	1	
Days 3-7	175,407	128	12	677	64	0.70	290,000	215	40	2			
Month 1	351,744	146	13	750	63	0.60	137,500	43	33	2			
Month 2	310,967	147	12	749	59	1.40	238,500	35	36	2			
Unsch	344,875	133	10	791	58	0.85	188,500	34	43	2			
Month 4	439,004	102	10	593	55	0.90	192,500	50	42	2			
Unsch	320,272	84	7	689	59	0.45	177,500	40	46	2			
Month 6													

Tables 2, 3, and 4 provide the HIV viral load (copies/mL), CD4 lymphocytes count (cells/mm^3), CD4%, CD8 lymphocytes count (cells/mm^3), CD8%, bilirubin (mg/dL), platelets count (cells/mm^3), CK-MB ratio of intracellular enzymes, ALT (U/L), AST (U/L), and HCV viral load (copies/mL).

Four of the first six patients (Patients 1, 4, 5, and 6) listed in Table 2 were tested to see if HIV could be cultured. The tests were negative each time. Patient 1 was tested at four, five, six, eight, and nine months after the first EWBH treatment to see if HIV could be cultured. The test was negative each time. Patients 4 and 5 were tested periodically and were still HIV culture negative at 6 months after EWBH. Patient 6 was HIV culture negative six months after EWBH. The test to see if HIV can be cultured was performed using an indirect immunofluorescence assay. This assay detects HIV using infected cultured lymphocytes. The infected cultured lymphocytes are incubated with patient serum and anti-HIV antibodies present within the serum bind to antigens expressed on the surface of the infected lymphocytes. These bound anti-HIV antibodies are then detected using labeled anti-human antibody.

According to the preferred embodiment, the patients will be screened for subsequent hyperthermic treatment as follows. The patients will be followed until they experience a confirmed 0.5 log or greater increase in HIV viral load either (1) from baseline, if no decline in viral load is achieved after receiving EWBH, or (2) from the lowest recorded HIV viral load following EWBH. In the event a patient experiences a confirmed 0.5 log or greater increase in HIV viral load, they will be re-screened for eligibility of EWBH, and if eligible, will be offered another single session of EWBH and followed per protocol. The criteria for re-treatment will be a 0.5 log increase in HIV viral load above baseline or nadir, whichever is greater. The details of the clinical protocol followed for the patients and the equipment used are presented below.

CLINICAL PROTOCOL

The purpose of this investigation was to assess the efficacy of a single EWBH treatment in individuals who were failing pharmaceutical therapies for HIV. Failing pharmaceutical therapies is defined as (A) an increase in HIV PCR viral load to $\geq$ 10,000 while on a stable antiviral regimen, and (B) the failure any two combination antiviral regimens composed of all three of the following categories: two nucleoside analogues, one non-nucleoside reverse transcriptase inhibitor and one protease inhibitor. A stable antiviral regimen is defined as no changes in antiretroviral regimen for sixteen weeks prior to screening for the

study. Antiviral regimens will usually give peak PCR lowering within 8 to 16 weeks after initiation.

In the event a patient experiences a confirmed 0.5 log or greater increase in viral load from baseline or nadir, they will be re-screened for eligibility for EWBH, and if eligible, will be offered another single session of EWBH and followed per protocol. All patients will have blood work drawn and analyzed at screening, during treatment, and at follow-up as per protocol. The criteria for re-treatment will be a 0.5 log increase in viral load above baseline or nadir, whichever is greater.

Analysis of primary objective parameters included HIV viral loading as measured by Polymerase Chain Reaction (PCR), HIV-RNA, and CD4 cell counts and percentages. Secondary objective parameters included the assessment of the cumulative incidence of opportunistic infections in the EWBH treated verses the control populations. Clinical utility, data assessing quality of life, were followed to evaluate significance of this treatment, pre and post therapy.

Prophylactic medication was allowed during the protocol period and appropriate treatment was given for opportunistic infections. Prophylactic medication to minimize the risk for recurrent Herpes infection was allowed. Any HIV/AIDS physical lesions present prior to therapy was measured and, if possible, photographed so that these lesions can be followed post treatment.

Patients fulfilled the following criteria to be eligible and had no ineligibility exclusions:

1. Documentation of positive test for Human Immunodeficiency Virus (HIV-1) Enzyme Linked Immunosorbent Assay (ELISA), confirmed by Western Blot.
2. Were failing recommended pharmaceutical therapy as defined by (A) an HIV PCR viral load of ≥ 10,000 while on a stable antiviral regimen (defined as no changes in antiretroviral regimen for sixteen weeks prior to screening for the study), (B) the failure of at least two combination antiviral regimens composed of 2 or more antiretroviral medications, and (C) prior use of at least two nucleoside analogues, one non-nucleoside reverse transcriptase inhibitor, and one protease inhibitor.
4. Karnofsky Performance status: ≥70%.
5. Male or female, age 18 – 60 years old, inclusive.

6. Granulocyte ≥500/mm3; White Blood Count (WBC) ≥1500/mm^3; platelet count ≥ 100,000/mm^3; hematocrit ≥30vol%, and hemoglobin ≥10g/dl.
7. Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), antithrombin III, fibrinogen, and thrombin time ≤ 20% of upper or lower limits of normal range.
8. Serum creatinine < 2.0 mg/dL.
9. Serum aspartate aminotransferase (SGOT, AST) and Serum alanine aminotransferase (SGPT, ALT) ≤ 5 X upper limit of normal.
10. Negative pregnancy test for females.
11. CD4+ lymphocyte helper cells ≤500 cells/mm^3.
12. Roche Amplicor HIV-1 RNA PCR ≥10,000 copies/ml.
13. Signed informed consent.
14. Stress Echocardiogram, or stress test and echocardiogram, or echocardiogram nucleotide studies with EF ≥45%, normal LV function and no evidence of coronary artery disease.
15. Forced Expiratory Volume (FEV1) ≥60% of expected function.
16. Negative CT scan of the brain with contrast.
17. Willingness to adhere to follow-up schedule.

Patients that exhibited any of the following were excluded from the protocol:

1. New York Heart Association (NYHA) classification III or IV.
2. History of a myocardial infarction, abnormal stress test suggesting ischemic changes, malignant, uncontrollable arrhythmia's or documented unstable angina within the last 12 months.
3. Major surgery within four weeks of protocol therapy.
4. History of central nervous system hemorrhage attributable to bleeding diathesis, or previously documented cerebrovascular accident.
5. Evidence of any active opportunistic infection. Patient must be at least four weeks status post therapy for opportunistic infection.
6. Allergic history to heparin, protamine, pork/beef products, fish, lidocaine or other anesthetic agents.
7. Uncontrolled hypertension, systolic BP 160 and diastolic BP 105.
8. Active illicit drug use determined by history.

9. Currently enrolled in other investigational clinical trial that would preclude participation in this protocol.

In the preferred embodiment, patients receiving EWBH treatment would continue their current drug regimens until EWBH treatment and then discontinue their drug regimens for the treatment and follow-up period. All EWBH-treated patients were be followed until they experienced a confirmed 0.5 log or greater increase in viral load either (1) from baseline, if no significant decline in viral load was achieved after receiving EWBH, or (2) from the lowest recorded viral load following EWBH. In the event an EWBH patient experienced a confirmed 0.5 log or greater increase in viral load from baseline or nadir, they were re-screened for eligibility of EWBH, and if eligible, were offered another single session of EWBH and followed per protocol. All patients were followed per protocol with serial collection of subjective and objective data. All data was be accumulated, tabulated and analyzed.

For purposes of analysis, all patients (EWBH and Control) remained on study until: (1) criteria for treatment is documented ($\geq$ 0.5 log increase in PCR from baseline or nadir); (2) end of the six-month follow-up following initial randomization; or (3) loss to follow-up, withdrawal, or death during six-month follow-up.

Analysis of primary objective parameters included HIV viral load as measured by Roche Amplicor HIV-RNA PCR, available from Roche Diagnostics, Nutley, New Jersey, lymphocyte subset profile and percentages (CD4). Secondary objective parameters included the assessment of the cumulative incidence of opportunistic infections in the patients. Clinical utility, data assessing quality of life were followed to evaluate significance of this treatment, pre and post therapy. The observed risks (i.e., device-related and treatment related adverse events) of EWBH were monitored in relation to the potential benefits of the therapy.

Each patient was informed of all procedures to insure that there would be compliance with the visits required for treatment and for the follow-up process. Patients received the best available care for medical problems arising during the study. Current medications were noted at the time of screening and reported on the case report form. Drugs administered or taken during the trial were recorded on the case report form, specifying the type of medication, dose, schedule, duration and reason for its use. All hospital admissions, clinic/office visits, incidence of opportunistic infections, including treatment given and duration,

were closely monitored and recorded on Serious Adverse Event (SAE) and Adverse Event (AE) forms.

Clinical history included the date of HIV/AIDS diagnosis, history of symptoms (dates and severity), and therapies previously administered, with duration of use and reasons for discontinuation. The history included all known allergies.

Clinical assessment included blood studies as listed in Table of Required Observations. Follow-up bloods were obtained at Day 1 post EWBH therapy and were repeated at follow-up clinic visits at day 3-7, months 1, 2, 4, and 6 months (± 1 week) (to the extent that the patient had reached these time points).

The following studies were performed in addition to the physical examination. Pre-procedure blood sampling was obtained on the morning of admission. Additional tests were repeated throughout the study (see Table of Required Observations). Tests and procedures were repeated as necessary to assess clinical toxicity.

1. Hematology:
   -Complete Blood Count (CBC, including WBC) with differential
   -Blood type (ABO Rh)
2. Coagulation:
   -Prothrombin time (PT), Partial thromboplastin time (aPTT), Antithrombin III, Thrombin time, Fibrinogen
3. General chemistries:
   -Sodium, Potassium, Chloride, CO_2, Calcium, Phosphorous, Magnesium, Glucose, Albumin, Creatinine, Cholesterol, Total protein, ALT, AST, Total bilirubin, Alkaline phosphatase, Creatinine Phosphokinase (CPK), Lactate Dehydrogenase (LDH), Blood Urea Nitrogen (BUN),
4. Cardiac assessment:
   -Stress Echocardiogram with Electrocardiogram (EKG)
5. Pulmonary assessment:
   -Chest X-ray (CXR), Pulmonary Function Tests (1 Second Forced Expiratory Volume, FEV1, and Forced Vital Capacity, FVC)
6. Renal Function:
   -BUN, Creatine
7. Neurologic assessment:
   -Thorough neurological physical examination

-Computed Axial Tomography (CAT) scan with contrast of the head

8. Immune system assessment:
-Lymphocyte phenotype profile, including CD4, and CD8.
-HIV RNA PCR (Roche Amplicor).

9. Chronic Hepatitis assessment:
-Hep C Qual. PCR
-Hep B Surface antigen
-HepB DNA PCR (if HBSAg positive)

10. Measurement and documentation of any lesions, if appropriate by photographs.

11. Measure of overall Karnofsky performance status

TABLE OF REQUIRED OBSERVATIONS

Test/Procedure	SCREEN[1,2]	Days[1,2]			Months[1,2]			
		0	1	3	1	2	4	6
Consent Form(s)	X							
ELISA / Western Blot	X							
HIV RNA PCR level	X	X	X	X	X	X	X	X
CD4/CD8 level	X	X	X	X	X	X	X	X
HepC Qual. PCR	X					X**		X**
Hep C bDNA (Bayer)	X***	X***	X***	X***	X***	X***	X***	X***
HepBSAg	X							
HepB DNA PCR****	X	X	X	X	X	X	X	X
HIV Genotype		X		X				
History and Physical	X	X	X	X	X	X	X	X
CXR	X							
Hematology	X	X	X	X	X	X	X	X
Blood Type	X							
Coagulation	X	X	X	X	X	X	X	X
Biochemical Profile	X	X	X	X	X	X	X	X
Cardiac Assessment	X							
Pulmonary Assessment	X							
Urine Analysis & Culture	X							
Neurologic Assessment	X							
Karnofsky Status	X	X		X	X	X	X	X
Lymph Node Biopsy[3]		X	X	X				X
Spinal Fluid Specimen[4]		X	X	X				X
Health Status Questionnaire	X			X	X	X	X	X

*Any test, measurement, or assessment was performed at any time, as clinically indicated.

**If HCV Qualitative PCR is negative

***If HepC Qualitative PCR is positive

****If HBSAg is positive at screening

[1]EWBH treatment group

[2]Control group

[3]Lymph Node biopsies were performed on the patients 1 to 7 days prior to the EWBH treatment, at day 1, day 3-7, and Month 6 or prior to re-treatment with EWBH (to the extent the patient had reached these time points).

[4]Lumbar puncture was performed to obtain spinal fluid from the EWBH treated patients 1 to 7 days prior to the EWBH treatment, at day 1, day 3-7, and Month 6 or prior to re-treatment with EWBH (to the extent the patient had reached these time points).

Health Status Questionnaire was completed @ screening, Day 3, and months 1,2,4,6.

The following protocol design was used in the hyperthermic treatment arm.

A. Pre Procedure:

After the history, physical examination, and laboratory procedures had been completed, and entry criteria satisfied, the patient was admitted to the hospital on the day of the procedure. Bloods were drawn according to the Table of Required Observations. Patient was Nothing Per Os (NPO) for at least 6 hours prior to the procedure. Preoperative antibiotics were given prophylactically for 24 hours.

B. Procedural Parameters:

Once in the Operating Room (OR) or treatment room s/he was placed upon the OR table and prepared for the procedure.

1. Description of Treatment Facility:

The OR or treatment room used for the procedure DID not have to be modified for this procedure. The operating table was equipped with a foam rubber mattress and/or pads for flexor point protection.

2. Patient Instrumentation for EWBH:

The following was placed in the operating room prior to EWBH:

i. Swan-Ganz EKG lead monitoring
ii. Peripheral intravenous (IV) lines (2),
iii. Radial artery catheter
iv. Pulmonary artery (Swan-Ganz type) thermistor catheter via central vein.
v. Oximeter.
vi. Urinary bladder catheter with thermistor.
vii. Rectal temperature probe.
viii Esophageal temperature probe (general anesthesia).
ix Tympanic temperature.
x. Bilateral femoral venous catheters was placed by a surgeon and connected to the hyperthermia unit

Temperature probes (esophageal, rectal, and tympanic) were calibrated, within 0.1°C, to a NIST traceable device.

3. Anesthesia:

Anesthetic management was the responsibility of the anesthesiologist administered appropriate agents according to the standard of care. The choice of anesthetic agent was determined based on individual patient profile. Either general anesthesia or sedative agents can be used.

To ensure an adequate hourly urine volume, a dopamine drip at 2-3 mcg/kg/min was used throughout the procedure and in the early postoperative period. Average urinary flow of 30 cc/hr minimum was targeted. Fluid replacement during the procedure was administered at the discretion of the operating team. Albumin and mannitol were not used during the hyperthermia treatment.

4. EWBH conduct, all parameters were entered on case report forms:

From the Swan Ganz catheter, serial readings of pulmonary systolic and diastolic pressures and blood temperature were recorded. Cardiac output (CO) as measured via the thermodilution catheter was measured prior to and following the treatment.

Each patient was continuously monitored at 5 minute intervals for temperature during the procedure. The perfusionist recorded all perfusion data on specific perfusion data forms. Other patient parameters were recorded on standard OR flow sheets.

Temperatures Monitored:

- Rectal (T_R), Esophageal(T_E), Tympanic (T_P), Pulmonary Artery (T_{PA}), Water Inlet/Heat Exchanger (T_W), Blood Outlet/Heat Exchanger (T_{Bld})

a. Preparation:

The perfusionist primed the circuit with an isotonic solution, and circulated until totally de-aired. The surgeon cannulated the femoral veins using open or percutaneous methods for connection with the extracorporeal circuit.

A predetermined dose of heparin required for extracorporeal circulatory bypass was calculated at 150 units/kg and administered in two 75 unit/kg doses with an Activated Clotting Time (ACT) determination before and after each dose. An ACT 2-1/2 to 3 times normal was maintained during EWBH. Further doses of heparin, if needed, were administered according to ACT measurement.

b. Heating Phase:

The time to reach a core temperature of 41.8° ± 0.2 was about 40 minutes.

i. EWBH was initiated at a blood flow rate of approximately <20% of the baseline cardiac output. The water circulating through the heat exchanger did not exceed 50°C for longer than 5 minutes.

ii. When either T_E or T_R (whichever is greater) reached 41.8°± 0.2 °C, the plateau phase was begun.

iii. When 40.0°C is reached, ice packs were placed under and/or around the patient's neck.

c. Plateau Phase:

i. Core body temperature (T_E, or T_R, whichever is greater) was maintained between 41.6- 42.0°C for 90 minutes. T_W was reduced so that neither T_E or T_R exceeded 42.0°C. Since body temperature cannot be

instantaneously changed, momentary excursions above 42.0°C were not be considered protocol deviations.

ii. Blood flow was altered to regulate blood and core temperature.

d. Cooling Phase:

Anticipated time to reach 39°C is 30 - 45 minutes.

i. Cooling was initiated at first by discontinuing the water flow for the first 20 minutes, cooling by ambient heat loss.

ii. After 20 minutes the thermostat was reset to 30^0C, and the water flow re-instituted.

iii. When T_R reached 39°C, bypass was discontinued.

iv. Decannulated and reversed heparin with protamine sulfate.

e. Once stable, the patient was transferred to the post anesthesia or recovery room.

REQUIRED OBSERVATIONS DURING EWBH BY PHASE

	Warming					Plateau							Cooling		
Test*	Pre/	0	15	30	45	0	15	30	45	60	75	90	15	30	
Post Blood gases		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrolytes	X			X				X				X		X	
Biochemistry	X													X	
Hematology	X														X
Urine Analysis & Culture	X														
CD4/CD8	X														
HIV RNA PCRX															
Hep C bDNA (Bayer)**	X														
Hep B DNA PCR***	X														
HIV-1 Genotype	X														
Coagulation	X														X
ACT only	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiac output		X-	-	-	-	-	-	-	-	-	-	-	-	-	-X
Urine output	X-	-	-	-	-	-	-	-	-	-	-	-	-X		
Pressure															
Arterial	X-	-	-	-	-	-	-	-	-	-	-	-	-X		
Pulmonary	X-	-	-	-	-	-	-	-	-	-	-	-	-X		
EKG	X-	-	-	-	-	-	-	-	-	-	-	-	-X		
Temperature	X-	-	-	-	-	-	-	-	-	-	-	-	-X		
CXR														X	
Lymph Node Bx[1]	X														
Lumbar Puncture[2]	X														

Legend: X = Discreet sample/monitor point

X—X = Continuous monitoring recorded at 15 ± 5 minute intervals

*Tests may be performed at any time following intervention.

** If Hep C Qual. PCR is positive at screening

***If Hep B DNA PCR is positive at screening

[1]Lymph node biopsy was performed on the patients 1 to 7 days prior to the EWBH treatment

[2]Lumbar puncture for spinal fluid analysis was performed in the patients prior to the EWBH procedure (1 to 7 days prior to the EWBH treatment)

C. Post-EWBH Patient Monitoring:

1. In the Post Anesthesia or Recovery Room, standard monitoring included:
   - -Continuous EKG monitoring
   - - 12 lead EKG strip if indicated
   - -Temperature, pulse, respirations and blood pressures (every 15 minutes for the first one and one-half hours, then every half hour for the next one and one-half hours),
   - -Urinary output
2. At the time of discharge from the hospital, a CXR was obtained to rule out the presence of pulmonary problems such as

pneumothorax, atelectasis, etc. Pressure dressing was removed from the femoral cannulation sites to confirm hemostasis.

3. Patients were discharged from the hospital when able to ambulate approximately 23 hours after admission.

Follow-up Visits

Follow-up visits were required at day 1 between day 3-7, and 1 month (± 7 days), 2 months (± 7 days), 4 months (± 7 days), and 6 months (± 7 days) after the EWBH treatment (to the extent the patient had reached these time points). At follow-up visits the patient was questioned about possible adverse reactions since their last visit, and any reaction described was recorded on the case report form. Blood was drawn for clinical laboratory tests according to the Table of Required Observations.

EQUIPMENT USED

The contents of the following U.S. patents and patent applications are hereby incorporated by reference into this application: (1) U.S. Patent No. 5,391,142, issued February 21, 1995, and entitled "Apparatus and Method for the Extracorporeal Treatment of the Blood of a Patient Having a Medical Condition," (2) U.S. Patent No. 5,674,190, issued October 7, 1997, and entitled "Extracorporeal Whole Body Hyperthermia Using Alpha-Stat Regulation of Blood pH and pCO_2," (3) U.S. Patent Application No. 09/334,224, filed June 16, 1999, entitled "Bladder Catheter for Hyperthermia System," and (4) U.S. Patent Application No. 09/334,520, filed June 16, 1999, entitled "Thermal Sensor for Hyperthermia System".

The hyperthermia equipment used was composed of three main components: (a) the console, (b) a heater/cooler unit and (c) the disposable blood contact circuit.

The console was composed of an extracorporeal, centrifugal pump device used for the operating and monitoring of the hyperthermia procedure. It contained the drive motor and controllers for the pump and electronics for monitoring the system parameters (temperature, pressure, and flow). The heater/cooler unit was used to raise or lower the patient's temperature and maintain a desired patient temperature through conductive heat transfer. Heated water was circulated through the heat exchanger to elevate the patient's temperature. Cool water was circulated through the heat exchanger to reduce the patient's temperature.

The disposable blood contact circuit was comprised of components for inducing and monitoring hyperthermia. In order to complete the circuit, vascular access was required. Blood left the patient via a venous cannula and PVC tubing which directed it to a centrifugal pump. From the pump, the blood was propelled through the heat exchanger where thermal exchange occurred, with the assistance of the heater/cooler. After the blood was heated it passed through a blood filter before returning to the patient via a second venous cannula. Circuit temperature was monitored by a calibrated thermistor probe placed within the outlet of the heat exchanger. This represented the highest blood temperature reading in the circuit. The blood temperature and those temperatures recorded from the heater/cooler as well as patient temperatures were the basis of the perfusion management of blood flow and heater/cooler temperature during the procedure.

Circuit flow was measured by an electrically isolated electromagnetic flowmeter built into the console, and a flow insert that was located in the blood circuit. Flow rates values have been determined experimentally to be approximately <20% of the baseline cardiac output. At these flow levels the rate of temperature rise to the patient was gradual enough not to cause biochemical parameters to change drastically. Blood flow rate adjustment was used with water bath temperature adjustment to fine tune the process and maintain the core body temperature within a narrow range for the appropriate time.

Circuit pressure monitoring was accomplished by the pressure electronics built into the console and a disposable transducer which was located at the input side of the heat exchanger. This position within the circuit allowed the operator to monitor resistance to flow downstream of the pump. Changes in the pressure reading were used as a diagnostic tool to determine circuit integrity and the state of anticoagulation. A connection was made between the three-way stopcock, at the transducer, and the two-way stopcock at the pump input. With the three-way stopcock turned to isolate the pump inlet pressure, the operator was able to recognize a possible malposition of the egress cannula. By utilizing this reading in conjunction with the pulmonary artery diastolic pressure it was possible to anticipate changes in the patient's volume status. A 40μm filter kept blood free of particulate matter.

The system was used to perform hyperthermia treatment of the patient's blood. The components and sub-assemblies were consolidated and coordinated to facilitate implementation of use. The apparatus included structures which defined an extracorporeal blood flow circuit. Such a circuit included a first cannula for use in cannulating a femoral vein of the patient. Such a cannula

defined a blood egress point. A second cannula was used for cannulating a different femoral vein of the patient, and the second cannula defined a blood ingress point. A discontinuous conduit was provided to interconnect, in part, the first and second cannulae. A conduit portion of an integrated, sterile module had interposed therein a pump, a heat exchanger for regulating the temperature of blood flowing through the conduit portion, and sensors for ascertaining the temperature, pressure, and flow rate of blood passing through the conduit portion. The apparatus, further, employed a controller for regulating the pump and temperature regulators in response to temperature, pressure, and blood flow rates sensed by the sensors.

A console was employed with the module having various controls. Such controls were used for selectively changing settings to achieve desired pressure and blood flow rate through the conduit portion.

The integrated, sterile module was a disposable component. As a result, the medical treatment facility inhibited the possibility of contamination of the blood of one patient by HIV positive blood of a patient previously treated, and of health care workers involved in the treatment.

In cannulating a patient for extracorporeal blood circulation, a blood flow circuit was defined between a first point of cannulation at a vein of the patient and a second point of cannulation at a vein of the patient. The patient's blood was then pumped through the circuit. As the blood passed through the circuit, it was heated to a first elevated temperature for a relatively short period of time. Thereafter, it was heated to a second elevated temperature, lower than the first elevated temperature, for a more extended period of time.

In an embodiment of the invention, the blood is heated to a first elevated temperature of between 42°C to 48°C. The blood could, typically, be maintained at the first elevated temperature for a period of time of about one half to one hour. Thereafter, the blood could be maintained at the second elevated temperature for a period of about one to two hours. The second elevated temperature, it is envisioned, could be between 42 to 44°C or 37°C to 39°C.

Referring now to the drawings wherein like reference numerals denote like elements through the several views, FIG. 2 shows diagrammatically the apparatus 10 used in the hyperthermia treatment of the patients as a procedure for addressing HIV infection. In FIG. 2, a femoral vein in the left leg was cannulated as a point of egress of blood from the patient's body (as at 16), and a femoral vein in the patient's right leg was cannulated as a point of ingress of the blood back into the patient (as at 18). It will be understood that these two specific points of cannulation 16, 18 are not exclusive and that other cannulation

locations are specifically contemplated. The locations illustrated in FIG. 2, however, have been found to be particularly appropriate, and ingress and egress points in different legs have been shown as being utilized so that a single leg of the patient is not compromised.

FIG. 2 illustrates the series blood flow circuit 14 which included first and second cannulae for cannulating the patient at two veins, as previously discussed. A conduit 24 having a discontinuity therein was provided to interconnect, in part, the first and second cannulae. An integrated, sterile module 26, as best seen in FIG. 1, was interfaced with the discontinuity in the discontinuous conduit 24 to complete the series blood flow circuit 14. The module 26 contained all of the components which were exposed to blood in the course of a treatment. It included a conduit portion 28 which was placed in communication with segments 30 of the discontinuous conduit 24 to complete the circuit 14.

The conduit portion 28 of the disposable module 26 had different components interposed therein. Blood was pumped from the egress point 16 of cannulation at a vein to a heat exchanger 32 by means of a pump 34 of appropriate construction. FIG. 2 illustrates the centrifugal pump 34 that was used, but it will be understood that this specific type of pump is not exclusive.

FIG. 2 illustrates a heat exchanger 32 down-flow from the pump 34. The heat exchanger 32 functioned to selectively elevate the temperature of the blood to a desired level. The blood, after passing through the heat exchanger 32, passed through a perfusate filter 36. At this location, the perfusate can be purged of any impurities.

A flow probe or sensor 38 was in the series flow circuit 14 down-flow from the perfusate filter 36. The probe 38 served to sense information with regard to the measure of flow rate of the perfusate passing through the circuit 14. FIG. 2 illustrates the pressure transducer 40 that was used in the circuit 14 down-flow from the flow sensor 38. While it is important to know flow rate of the perfusate through the circuit 14, it is also important to know the pressure through the system also. Consequently, the patient being treated can be adequately protected.

FIG. 2 also illustrates the temperature sensor 42 that was used in the circuit 14. The sensor 42, of course, served to provide information with regard to the temperature of the blood flowing through the circuit 14.

FIG. 2 also shows a branch 44 of the circuit 14 which recirculated excess perfusate, not needed to be fed back into the patient, back to the pump 34 for recirculation. The recirculation branch 44 was also used during initial setup.

Also illustrated are a series of tubing clamps 46. Such clamps 46 serve, basically, as occluders which can be disposed to pinch tubing segments to preclude flow therethrough. In FIG. 2, the three such tubing clamps 46 that were used are illustrated. A first was immediately down-flow of the egress point on the patient. A second was located immediately prior to the location at which the blood reenters the patient's body. The third was positioned in the recirculation segment of the circuit 14.

FIG. 1 illustrates, as previously discussed, an integrated, sterile module 26 in which are disposed all of the components described with reference to FIG. 2 as being exposed to blood in the blood flow circuit 14. FIG. 1 also, however, illustrates the non-disposable base unit that was used including a chassis 60 which removably mounts the integrated, sterile module 26. FIG. 1 further shows that the base unit included a console or controller unit 62 for controlling operation of the hyperthermia procedure being performed. The console 62 functioned to regulate and maintain perfusate flow rate, pressure, and temperature at desired levels.

The console 62 had a series of digital display windows 64. Such windows 64 read temperature, pressure, and flow rate and displayed those parameters for both actual sensed values and inputted alarm range settings. Each display 64 was provided with a series of visual alarms (i.e., LED's 66) for signaling when, for example, a desired range within which temperature, flow rate, or pressure, is intended to be maintained, was exceeded. A series of alarm setting controls 68 were also shown as being provided. Each window 64 had corresponding upper and lower range controls and an intermediately positioned toggle switch 70. The toggle switch 70 could be toggled between positions representative of upper and lower range settings. When in an upper range setting, for example, the appropriate dial 72 could be maneuvered to adjust the upper range limit.

Finally, the control panel 74 of the console 62 had a lower row of dials, displays, etc. These components included a timer 76, rate and amplitude controls 78 for additional modes of operation (such as a pulsatile mode), and an electronic filter 80 for filtering aberrant amplitude signals regarding, for example, pressure in the circuit 14, etc.

In the structure illustrated in FIG. 1 and used to treat the patients, it is intended that the heater/cooler (not shown) for providing external fluid to the heat exchanger 32 would not comprise part of the console 62. Heat exchange was implemented in a collateral manner known in the prior art.

While not specifically shown in FIG. 1, the console 62 contained therewithin a motor 82 which interfaces, through a wall, with the perfusate pump

34. This was done by providing the motor 82 with a magnetic rotor. As the motor 82 was driven, the rotor was caused to be rotated also. A magnetic element was provided in the pump 34, and such a magnetic element interfaced, through the wall, with the magnetic rotor. Driving of the rotor, in turn, translated to operation of the pump 34 to a desired level.

FIG. 3 illustrates schematically how the pump 34, was controlled in response to pressure and flow rate levels sensed by respective sensors 38, 40. Those figures show the integrated, sterile module 26 and the components enclosed therewithin by a dotted line.

In utilizing the system for hyperthermia treatments, the patient was cannulated in the manner discussed above. Initially, the patient was out of the circuit 14, and flow bypassed the patient. This was effected by manipulation of the appropriate tube clamps 46 to effect flow through the bypass branch circuit 44.

A selector switch 84 was manually positioned so that feedback was provided from either the motor 82, the pressure transducer 40, or the flow probe 38. Input from the appropriate feedback component passed through the selector switch 84 to a servo-amplifier 86. The amplifier 86, in turn, inputted information to control the pump speed in an appropriate fashion to accomplish desired flow and pressure parameters.

FIG. 3 also illustrates a variable resistor 88 which was manipulated in initiating the setting of a particular parameter. The parameter was set and, after the system was appropriately calibrated, the patient was introduced into the flow system 14. Thereafter, continuous monitoring was performed of temperature, pressure, and flow rate. If the alarm system indicated that a parameter had gone outside the desired range, appropriate action was taken to bring the parameter back within the range.

During hyperthermia, pCO_2 varies directly with a change in body temperature. It is desirable to hold the bloods CO_2 content constant during alpha-stat regulation, thereby requiring an inverse relationship between air convection requirements and body temperature. Alpha-stat maintains constant CO_2 by regulating pCO_2. Hence, utilizing the alpha-stat technique for blood gas management is advantageous in that the pH gradient across the cellular membrane is preserved throughout the range of temperatures encountered during hyperthermia. This alpha-stat regulation of blood pH and pCO_2 were used in treating the patients.

By direct control of pulmonary ventilation through manipulation of respiratory rate, the pCO_2, the total CO_2, and the pH were maintained

throughout the procedure according to alpha-stat parameters, ensuring that electrolyte balance was maintained throughout. No electrolyte replacement was required in any patient during the procedure, nor was there ever a need to administer sodium bicarbonate for metabolic acidosis.

The blood flow circuit comprised a Blood Gas Analyzer (BGA). Within the BGA is an analyzer which analyzes the blood gases, including the blood pH and pCO_2 through infrared or chemical analysis. A pulse oximeter attached to the patient through suitable means, measured the pO_2 of a patient's blood. The microprocessor then analyzed the data associated with the blood's pH, pCO_2, pO_2 and calculated the base excess of the blood normalized at 37°C. The microprocessor was programmed to then automatically adjust the respiratory rate of the patient and either the amount of $NaHCO_3$ or acidotic crystalloid solution (which affects the HCO_3^- ion concentration) being introduced into the patient's blood. This was accomplished by adjusting the respiratory rate of the patient through ventilation or medications.

The respiratory management of the blood at constant CO_2 content, while the temperature was changed, maintained a constant alpha thereby stabilizing the biochemical reactions fundamental to the metabolic welfare of components of the patient's blood. The sodium bicarbonate buffering system was based upon the following equation:

$$H^+ + HCO_3^- \sim H_2CO_3 \sim H_2O + CO_2$$

Acidosis ($\downarrow$pH) occurs when there is an increase of H+ (metabolic) and/or CO_2 (respiratory). Respiratory acidosis was treated with changes in depth of ventilation or ventilatory rate. Metabolic acidosis was treated with the administration of sodium bicarbonate ($NaHCO_3$). "Bicarb" dissociates into Na+ and HCO_3^- which combines with H+ to form CO_2 and H_2O.

The blood gases, pH, pO_2, pCO_2, and HCO_3^- concentration were obtained by direct measurement. Base excess (BE) is a derived parameter based upon the relationship between the measured pCO_2, and HCO_3^- concentration, and is calculated relative to the normal HCO_3^- centration values: 24 mEq/L in arterial blood and 26 mEq/L in venous blood.

OPTIONAL EQUIPMENT THAT WAS NOT USED

A thermal sensor and bladder catheter that were not used to treat the patients are described below.

THERMAL SENSOR

An improved temperature monitoring device suited to extracorporeal whole body hyperthermia can be used.

The sensor described is connected to the blood flow circuit near the patient. The temperature sensor has a very small mass and is place on a strut. The strut places the thermal sensor in the laminar blood flow of a duct or fitting. In this fashion, a fast reacting thermal assessment may be made of blood temperature as blood enters or leaves the body.

FIG. 4 illustrates a temperature probe 133 for supporting the temperature sensor 130 in the flow of blood moving through a hyperthermia system. As shown in FIG. 4, the probe 133 includes a tube or flow-directing passage 140 having a wall defining an interior lumen 141. Although a cylindrical shape is shown and is preferred to minimize wetted surface area, other cross-sectional shapes are operable. As shown in FIG. 4, the cross-sectional area of the lumen 141 remains constant in the direction of flow indicated by arrow 138. It should be appreciated that the lumen 141 may decrease in cross-sectional area in the direction of flow to maintain laminar flow past the strut 134.

A temperature sensor 130 is attached to the strut 134. Preferably, the strut 134 is shaped and positioned such that the sensor 30 supported thereon is placed in a region of laminar flow and preferably near a location of maximum flow velocity. A region of laminar flow is illustrated in the velocity profile 136. More specifically, the strut 134 is shaped and positioned such that at least a portion of strut 134 lies upstream of the site at which the strut 134 attaches to or passes through the tube 140. The preferred strut 134 has a generally arcuate shape along its length. As shown in the embodiment illustrated in FIG. 4, the strut 134 has a terminating tip 145 that is positioned near the axial center of the tube 140 where the blood flow achieves maximum velocity. In this fashion the sensor 130 is located in the maximum flow zone in the device and can sense subtle changes in blood temperature. By positioning the sensor "in-line", or in the flow of blood as it passes through the system, advantages are achieved. For example, the laminar flow prevents disruption of the blood and temperature change due to mixing. This factor combined with the fast response small thermal mass sensor 130 improves control of body temperature.

The preferred form of the probe 133 includes fittings which may be barbed. These allow the device to be positioned close to the patient. It is believed that monitoring in close proximity to the patient is desirable to minimize heat loss to the environment.

More than one sensor can be used in a hyperthermic system. The use of a second sensor increases the ability of the system to accurately monitor and control temperature.

The sensors 130 and 132 may be of any temperature-sensing type, such as thermistors, thermocouples, and the like.

BLADDER CATHETER

An improved catheter can be used in the whole body hyperthermia system. In use, the catheter is suspended in the bladder of the patient. A cuff on the catheter inflates after the catheter is inserted in the bladder to assist in positioning and securing the catheter. The catheter has a temperature sensor proximal of the inflatable cuff to measure body temperature at the urinary sphincter muscle. The sensor is located relative to the cuff a distance know to generally correspond to the typical distance between the bladder and the sphincter muscle in humans. This distance is known to be approximately the same amongst humans regardless of size.

In an alternative catheter, a second temperature sensor is placed distal of the inflatable cuff and thus monitors the temperature of the urine pool in the bladder. Each of the measurements from the first and second temperature sensors has a different time constant depending on the volume of urine in the bladder, and the level of perfusion in the sphincter. Data from these two sensors, the differences between the readings, and the time-dependent variation of these two sensors can contribute to the overall efficacy of the device.

An exemplary version of the bladder catheter is shown in the figures in which like reference numerals refer to equivalent structure throughout.

FIG. 5 shows a bladder temperature probe 230 having an elongate body 244 and terminating in a proximal end 246 and further having a distal tip 248 and a first temperature sensor 232, which may be of any conventional type, including thermistors, thermocouples or other solid state temperature sensors. A drainage lumen 236 communicates with a distal opining 238 to allow fluid to be withdrawn from the bladder 231 or to allow fluid, such as saline, to be infused into the bladder. An inflatable distal cuff 240 positions the catheter and prevents its removal from the bladder while the cuff is inflated. The sensor 232 and the inflatable cuff are spaced and oriented such that when the inflatable cuff 240 holds the probe 230 in position in the patient's bladder 231, the sensor 232 is located proximal of the urinary sphincter muscle 242. Temperature information gathered at this site from the surrounding tissue is likely to be reliable and

somewhat less subject to rapid fluctuation than a temperature reading taken from other locations, such as the urine pool.

In an alternate catheter, illustrated in FIG. 6, the catheter carries a second temperature sensor 234. In practice, the cuff positions the second temperature sensor 234 in the bladder urine or fluid pool while the first sensor 232 is located adjacent the musculature near the sphincter 242. It is expected that the two sensors will vary in measured temperature as the effective time constants for the two locations differ. These two temperatures and relative rates of their variation contribute to the efficacy of body temperature control.

Computerized controls can be added to all of the equipment described above.

The above description is provided for the purpose of describing embodiments of the invention and is not intended to limit the scope of the invention in any way. It will be apparent to those skilled in the art that various modifications and variations can be made without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

What is claimed is:

1. A method for treating a patient infected with human immunodeficiency virus (HIV) comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time, wherein the core temperature is raised to a temperature range and a duration sufficient to: (1) eliminate or reduce viable HIV to an extent such that a culture of HIV from the patient is negative around three months after the core temperature of the patient has been raised and returned to normal at least one time and (2) result in an increase in the CD8% around one month after the core temperature of the patient has been raised and returned to normal at least one time.

2. The method of claim 1, wherein the core temperature of the patient is raised and returned to normal one time.

3. The method of claim 1, wherein the core temperature of the patient is raised and returned to normal two or more times.

4. The method of claim 1, wherein the core temperature is raised by circulating the patient's blood from the patient, through an extracorporeal blood flow circuit, and back to the patient, wherein the blood returned to the patient has been heated within the blood flow circuit to an elevated temperature range.

5. The method of claim 1, wherein the patient is failing multi-pharmaceutical treatment for HIV.

6. The method of claim 1, wherein the patient is not failing multi-pharmaceutical treatment for HIV.

7. The method of claim 1, wherein the core temperature is raised to a temperature range of from 38 to 48°C.

8. The method of claim 1, wherein the CD8% has increased 5 percent or more one month after the core temperature of the patient has been raised and returned to normal said at least one time.

9. The method of claim 1, wherein the CD8% has increased 10 percent or more one month after the core temperature of the patient has been raised and returned to normal said at least one time.

10. The method of claim 1, wherein the CD8% has increased 20 percent or more one month after the core temperature of the patient has been raised and returned to normal said at least one time.

11. The method of claim 1, wherein the CD8% is measured before raising the core temperature of the patient and after the core temperature of the patient has been raised and returned to normal said at least one time.

12. The method of claim 11, wherein the CD8% is measured one day after the core temperature of the patient has been raised and returned to normal said at least one time.

13. The method of claim 11, wherein the CD8% is measured one month after the core temperature of the patient has been raised and returned to normal said at least one time.

14. The method of claim 1, wherein the ability to culture HIV from the patient is assessed from around three months to around six months after the core temperature has been raised and returned to normal said at least one time.

15. The method of claim 1, wherein a culture of HIV from the patient is negative around six months after the core temperature has been raised and returned to normal said at least one time.

16. The method of claim 1, wherein a culture of HIV from the patient is negative around one year after the core temperature has been raised and returned to normal said at least one time.

17. The method of claim 1, wherein a culture of HIV from the patient is negative around two years after the core temperature has been raised and returned to normal said at least one time.

18. A method for auto-inoculating a patient infected with human immunodeficiency virus (HIV) comprising raising the core temperature of the

patient and then returning the core temperature of the patient to normal at least one time, wherein the core temperature is raised to a temperature range and a duration sufficient to: (1) eliminate or reduce viable HIV to an extent such that a culture of HIV from the patient is negative around three months after the core temperature of the patient has been raised and returned to normal at least one time and (2) result in an increase in the CD8% around one month after the core temperature of the patient has been raised and returned to normal at least one time, and

wherein the patient has a measurable viral load of HIV around three months after the core temperature of the patient has been raised and returned to normal at least one time.

19. The method of claim 18, wherein a culture of HIV from the patient is negative and the patient has a measurable viral load of HIV around six months after the core temperature has been raised and returned to normal said at least one time.

20. The method of claim 18, wherein a culture of HIV from the patient is negative and the patient has a measurable viral load of HIV around one year after the core temperature has been raised and returned to normal said at least one time.

21. The method of claim 18, wherein a culture of HIV from the patient is negative and the patient has a measurable viral load of HIV around two years after the core temperature has been raised and returned to normal said at least one time.

22. The method of claim 18, wherein the viral load of HIV is measured using a reverse transcriptase-polymerase chain reaction test.

23. The method of claim 19, wherein the viral load of HIV is measured using a reverse transcriptase-polymerase chain reaction test.

24. The method of claim 20, wherein the viral load of HIV is measured using a reverse transcriptase-polymerase chain reaction test.

25. The method of claim 21, wherein the viral load of HIV is measured using a reverse transcriptase-polymerase chain reaction test.

26. The method of claim 1, wherein the patient's viral load of HIV is determined at least once before the core temperature has been raised said at least one time.

27. The method of claim 1, wherein the patient's viral load of HIV is determined at least once after the core temperature has been raised and returned to normal said at least one time.

28. The method of claim 1, further comprising treating the patient with a pharmaceutical indicated for HIV.

29. The method of claim 28, wherein the pharmaceutical is administered more than three months after the core temperature of the patient has been raised and returned to normal at least one time.

30. The method of claim 28, wherein the raising the core temperature of the patient and then returning the core temperature of the patient to normal is alternated with treating the patient with the pharmaceutical.

31. The method of claim 1, wherein at some time subsequent to three months after the core temperature of the patient has been raised and returned to normal at least one time, a culture of HIV from the patient is positive and the patient is then treated with a pharmaceutical indicated for HIV.

32. The method of claim 1, wherein at some time subsequent to three months after the core temperature of the patient has been raised and returned to normal at least one time, a culture of HIV from the patient is positive and the patient is then re-treated with the method for treating a patient infected with HIV.

33. The method of claim 28, wherein the patient is treated with a single pharmaceutical indicated for treating HIV.

34. The method of claim 28, wherein the patient is treated with two or more pharmaceuticals indicated for treating HIV.

35. The method of claim 28, wherein the pharmaceutical is administered before raising the core temperature of the patient said at least one time.

36. The method of claim 28, wherein the pharmaceutical is administered while the core temperature of the patient is raised.

37. The method of claim 28, wherein the pharmaceutical is administered after the core temperature of the patient has been raised and returned to normal said at least one time.

38. The method of claim 28, wherein the pharmaceutical is administered: (i) before raising the core temperature of the patient said at least one time; (ii) while the core temperature of the patient is raised; (iii) after the core temperature of the patient has been raised and returned to normal said at least one time; or (iv) combinations thereof.

39. The method of claim 28, wherein the pharmaceutical is administered before raising the core temperature of the patient said at least one time, while the core temperature of the patient is raised, and after the core temperature of the patient has been raised and returned to normal said at least one time.

40. The method of claim 28, wherein the pharmaceutical is selected from interferons, protease inhibitors, cytokines, nucleoside analog reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, or any combination of antiviral drugs.

41. The method of claim 28, wherein the pharmaceutical is selected from ribavirin, lamivudine, interferon alfacon-1, interferon alfa-2a, interferon alfa-2b, interferon-alfa-nl, thymosin alpha-1, interleukin-2, interferon alpha-n3, ketoprofen, interferon beta-la, interferon gamma-1b, interleukin-12, histamine dihydrochloride, thymalfasin, zidovudine, didanosine, zalcitabine, stavudine, abacavar, nevirapine, delaviridine, efavirenz, ritonavir, indinavir, nelfinavir, saquinavir, amprenavir, or combinations thereof.

42. The method of claim 28, wherein the pharmaceutical is selected from an interferon, ribavirin, or lamivudine.

43. The method of claim 28, wherein the pharmaceutical is an alpha interferon.

44. The method of claim 1, wherein the patient has an acute HIV infection.

45. The method of claim 1, wherein the patient has a latent HIV infection.

46. The method of claim 1, wherein the patient is co-infected with a pathogen.

47. The method of claim 46, wherein the pathogen is a virus.

48. The method of claim 46, wherein the pathogen is a spirochete or bacterium.

49. The method of claim 47, wherein the virus is a heat labile virus.

50. The method of claim 49, wherein the heat labile virus is selected from herpesviruses, hepadnaviruses, togaviruses, flaviviruses, coronaviruses, rhabdoviruses, filoviruses, paramyxoviruses, othomyxoviruses, bunyaviruses, arenaviruses, or retroviruses.

51. The method of claim 49, wherein the heat labile virus is selected from hepatitis B virus, hepatitis C virus, Epstein-Barr virus, cytomegalovirus, or varicella-zoster virus.

52. The method of claim 48, wherein the pathogen is a spirochete selected from the genus treponema, borrelia, or leptospira.

53. The method of claim 48, wherein the pathogen is a spirochete selected from *Treponema pallidum, Treponema pertenue, Treponema carateum, Treponema pallidum endemicum, Borrelia burgdorferi, Borrelia hermsii,* or *Leptospira interrogans.*

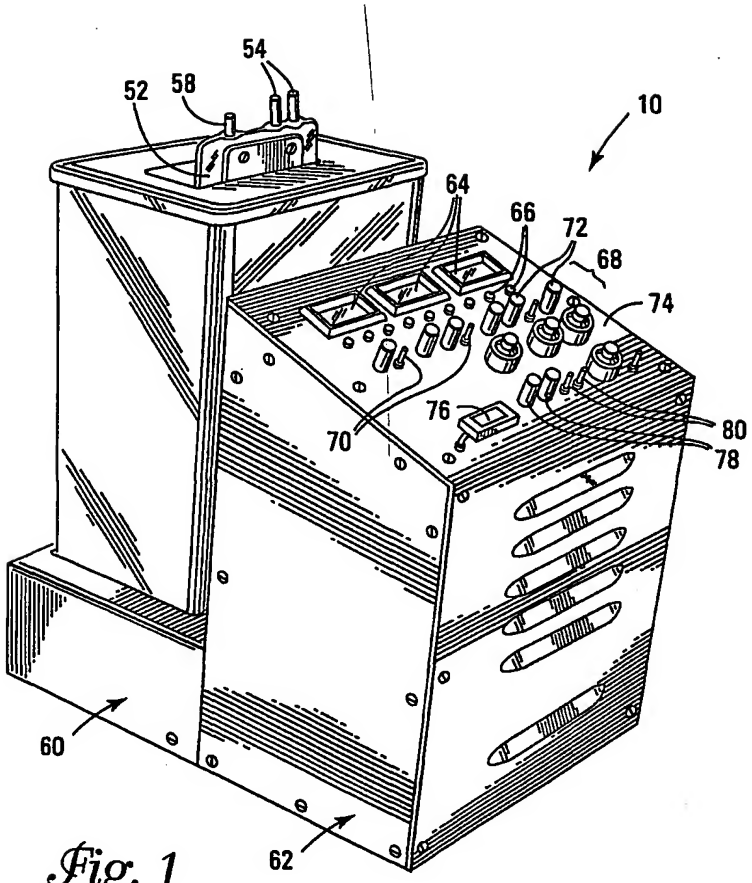

Fig. 1

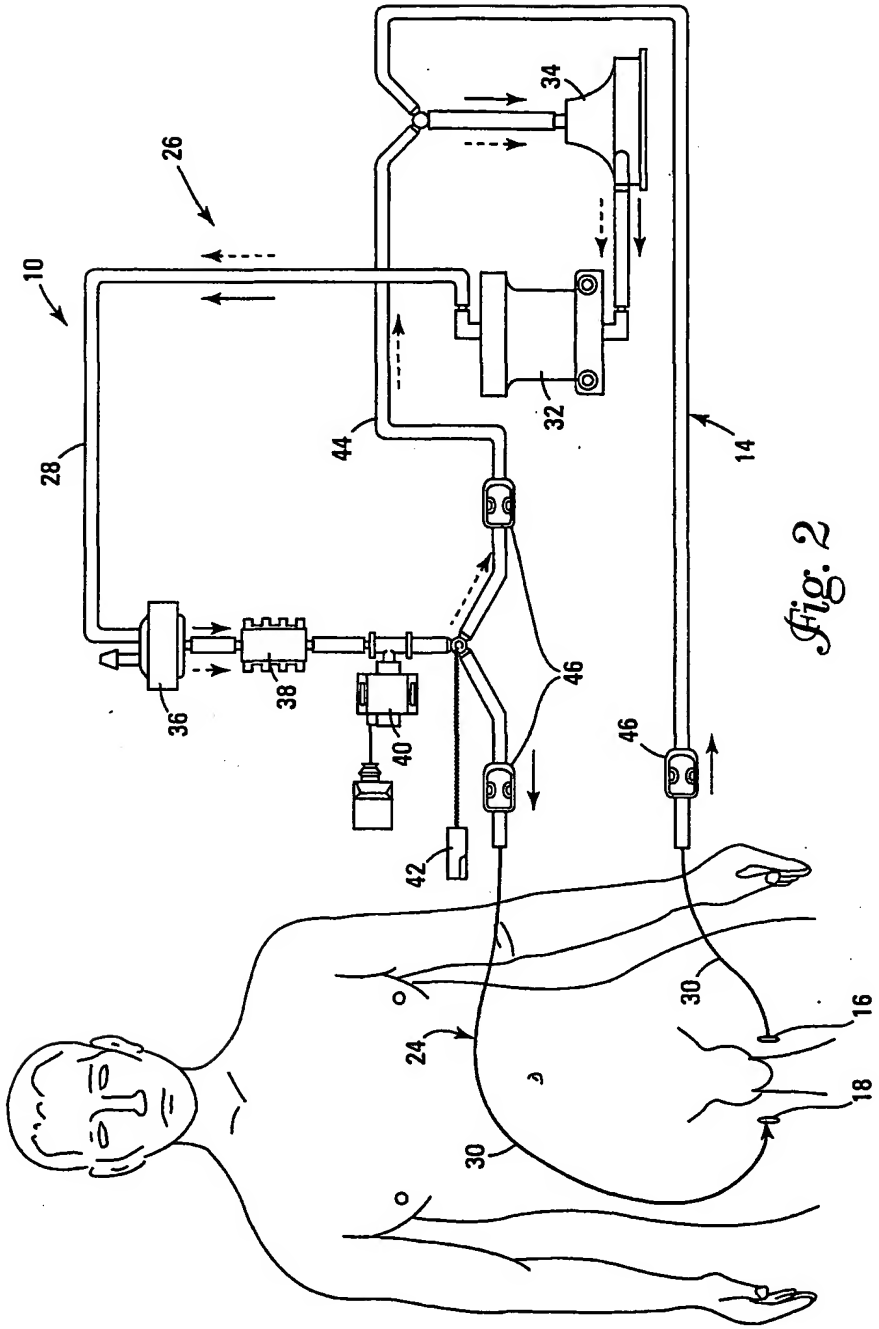

Fig. 2

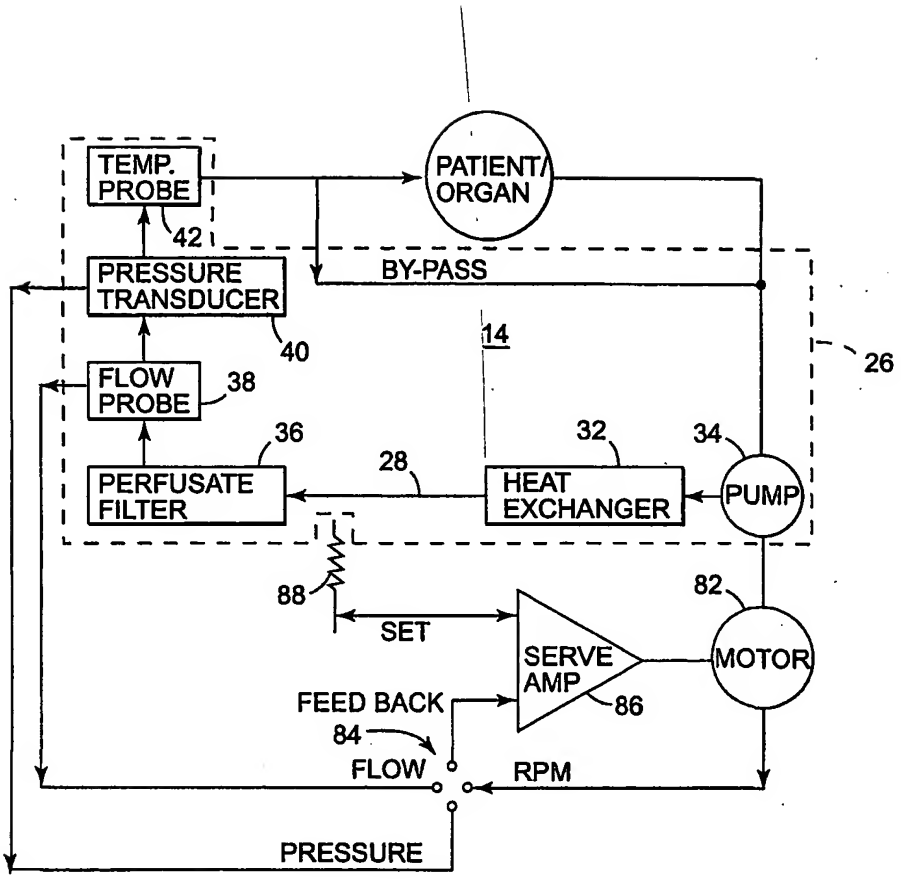
TEMP. PROBE
42
PATIENT/ ORGAN
PRESSURE TRANSDUCER
40
BY-PASS
14
26
FLOW PROBE
38
36
32
34
28
PERFUSATE FILTER
HEAT EXCHANGER
PUMP
88
82
SET
SERVE AMP
MOTOR
FEED BACK
86
84
FLOW
RPM
PRESSURE

Fig. 3

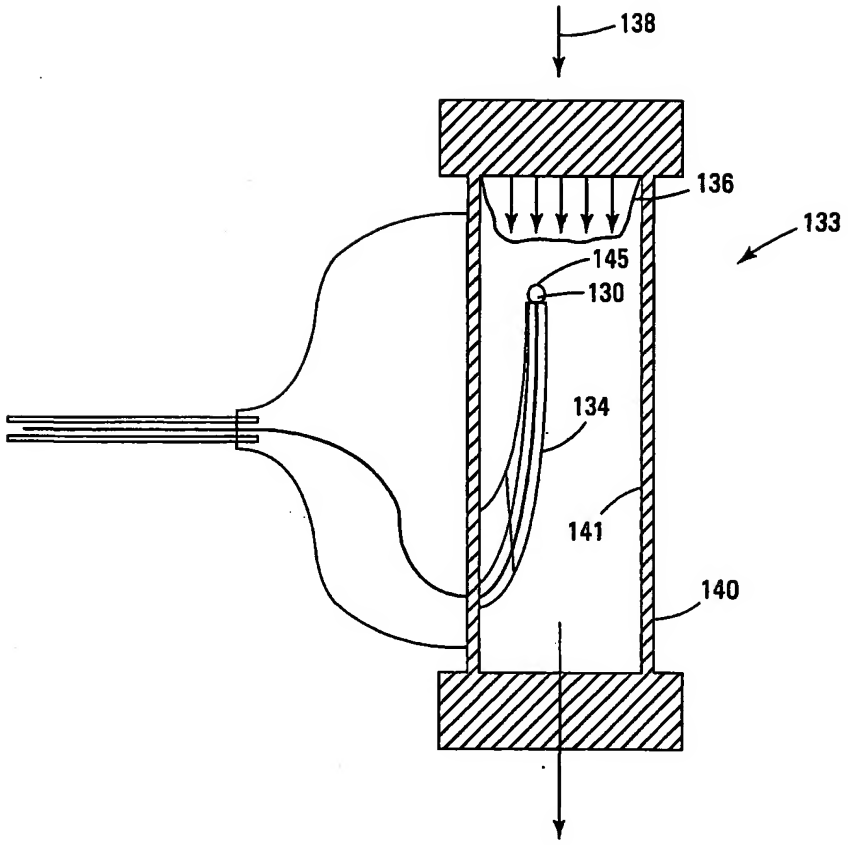

Fig. 4

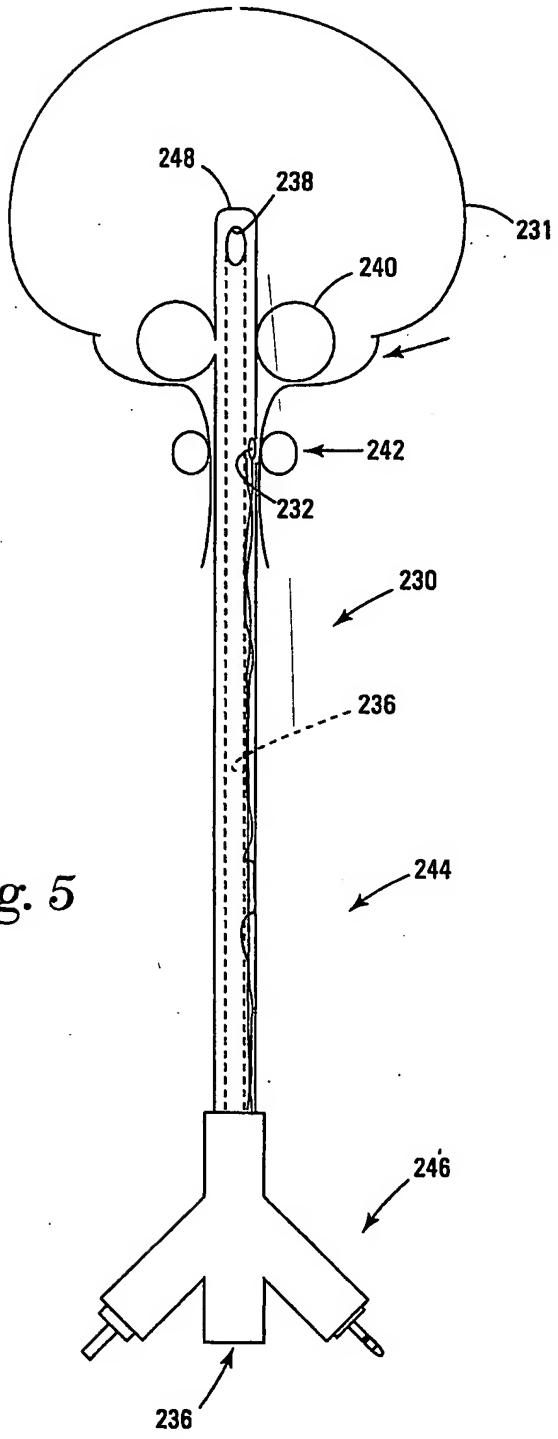

Fig. 5

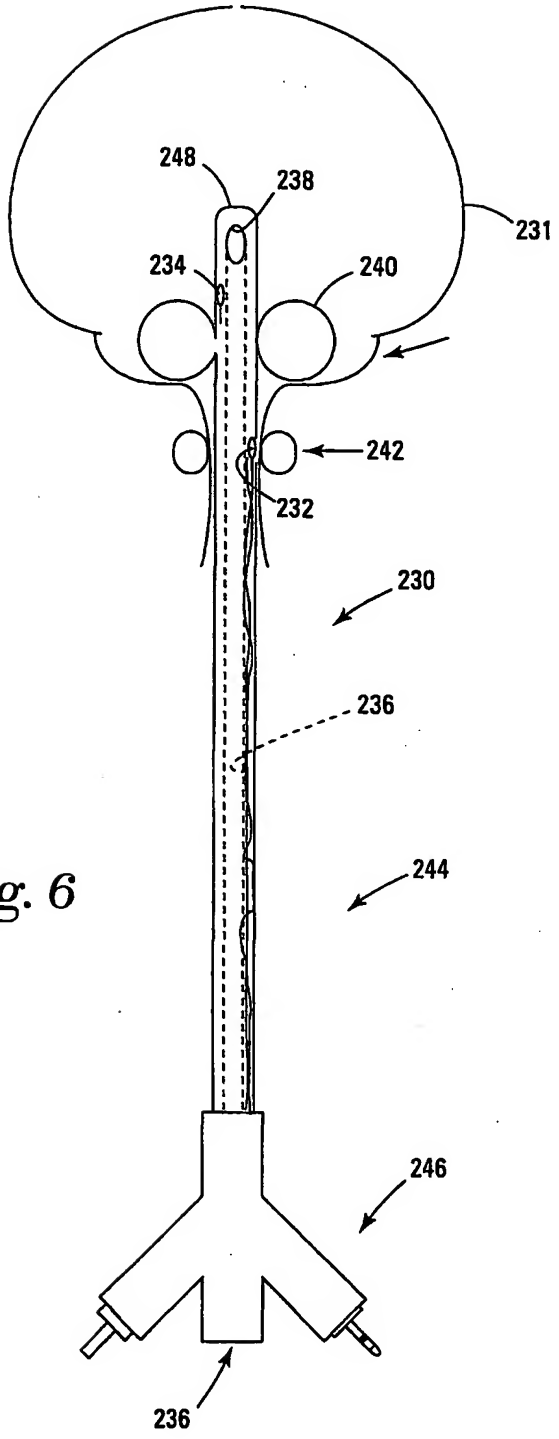

Fig. 6